Proposed Registration Decision PRD2010-12

Oxalic Acid Dihydrate

(publié aussi en français)

21 May 2010

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

Publications
Pest Management Regulatory Agency
Health Canada
2720 Riverside Drive
A.L. 6604-E2
Ottawa, Ontario
K1A 0K9

Internet: pmra.publications@hc-sc.gc.ca
healthcanada.gc.ca/pmra
Facsimile: 613-736-3758
Information Service:
1-800-267-6315 or 613-736-3799
pmra.infoserv@hc-sc.gc.ca

Canada

HC Pub: 100240

ISBN: 978-1-100-15729-0 (978-1-100-15860-0)
Catalogue number: H113-9/2010-12E (H113-9/2010-12E-PDF)

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Overview

Proposed Registration Decision for Oxalic Acid Dihydrate

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Oxalic Acid Dihydrate Technical and Oxalic Acid Dihydrate, containing the technical grade active ingredient oxalic acid dihydrate to control Varroa mites in honeybee colonies.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Oxalic Acid Dihydrate Technical and Oxalic Acid Dihydrate.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

Before making a final registration decision on oxalic acid dihydrate, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on oxalic acid dihydrate, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is Oxalic Acid Dihydrate?

Oxalic acid dihydrate is a dicarboxylic acid, which is a relatively strong organic acid. Oxalic Acid Dihydrate is used in honeybee colonies to control Varroa mites using two different application methods, as a solution by the trickle treatment method, and as a solid by the vaporisation method. Applications are made in the late fall to early spring, when little to no brood is present in the hive and honey supers are not in place.

While the mode of action of Oxalic Acid Dihydrate is not entirely understood, it appears to be mainly due to the low pH of the acid, which results in contact toxicity (physical injury of mites due to low pH). With the trickle-method of application, Oxalic Acid Dihydrate is dissolved into a 1:1 sugar:water solution, which is directly applied to the infested bees. The bees can tolerate the concentration of oxalic acid in the applied solution, but the Varroa mites cannot. With the vaporisation method of application, Oxalic Acid Dihydrate crystals are heated using a specialized application device until they liquefy and vaporise. Oxalic acid vapour fills the hive and all the bees and hive interior surfaces are covered with a very thin layer of Oxalic Acid Dihydrate crystals. While these fine crystals are tolerated by the bees, they are toxic to the Varroa mites.

Health Considerations

Can Approved Uses of Oxalic Acid Dihydrate Affect Human Health?

Oxalic Acid Dihydrate is unlikely to affect your health when used according to label directions.

Exposure to oxalic acid dihydrate may occur when handling and applying the end-use product, Oxalic Acid Dihydrate. When assessing health risks, two key factors are considered: the levels where no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (e.g. children and nursing mothers). Only uses for which the

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Since the technical grade active ingredient, oxalic acid dihydrate, is highly acutely toxic and corrosive to both the eye and skin, the statements, "DANGER – POISON", "DANGER – CORROSIVE TO EYES", and "DANGER – SKIN IRRITANT" have been included on the principal display panel of the general label and "Fatal or poisonous if swallowed", "DO NOT get in eyes", "CORROSIVE to the eyes", "DO NOT get on skin or clothing", "Corrosive to the skin", and "Avoid inhaling/breathing dust or fumes" have been included in the PRECAUTIONS section of the secondary display panel of the general label.

Residues in Water and Food

Dietary risks from food and water are not of concern.

It is anticipated that the amount of oxalic acid dihydrate present as a residue after application of the end-use product will not likely exceed the range of naturally occurring concentrations found in honey or vegetables. The direct application of oxalic acid dihydrate to beehives means that exposure to sources of drinking water will be negligible. Therefore, the use of oxalic acid dihydrate is not expected to result in dietary risk from food and/or water.

Occupational Risks From Handling Oxalic Acid Dihydrate

Occupational risks are not of concern when Oxalic Acid Dihydrate is used according to label directions, which include protective measures.

Pesticide applicators handling and applying Oxalic Acid Dihydrate to bee hives, can come in direct contact with oxalic acid dihydrate on the skin and in the eyes, as well as by accidental ingestion and inhalation. The current label statements adequately mitigate the concern of exposure to the applicators.

It is expected that only workers will be permitted access to the treated areas, thus the potential for bystander exposure is expected to be minimal and not of concern.

Environmental Considerations

What Happens When Oxalic Acid Dihydrate Is Introduced Into the Environment?

Oxalic acid is a naturally occurring compound that transforms rapidly under environmental conditions. Exposure of the chemical to the environment is expected to be limited during the use of Oxalic Acid Dihydrate for control of Varroa mite in beehives. The product is applied as a liquid or vapour to an affected colony; environmental exposure would occur primarily through spillage or leakage during application. Based on limited exposure, the chemical's natural occurrence and the likelihood for relatively rapid

transformation under environmental conditions, the proposed use of Oxalic Acid Dihydrate is not expected to pose a significant risk to the environment. Therefore, further review of the environmental chemistry, fate, and toxicology of Oxalic Acid Dihydrate was not considered necessary.

Value Considerations

What Is the Value of Oxalic Acid Dihydrate?

Oxalic Acid Dihydrate has value for control of Varroa mite in honeybee colonies. Evaluated data demonstrated that Oxalic Acid Dihydrate can provide 90-99% control of Varroa mites in honeybee colonies when either the trickle treatment or vaporisation application methods are used when little to no honeybee brood is present in the hives (i.e. late fall to early spring).

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the labels of Oxalic Acid Dihydrate Technical and Oxalic Acid Dihydrate to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

Because there is a possibility of accidental oral, dermal, and inhalation exposure by workers, individuals should observe all precautionary and first aid statements on the product label. The label-required wearing of personal protective equipment by workers and the requirement to conduct activities in well ventilated areas are expected to minimize the potential for exposure to oxalic acid dihydrate. Based on the limited use pattern to bee hives, bystanders are not expected to be exposed to oxalic acid dihydrate.

Environment

No environmental risk-reduction measures are required. Standard label statements to protect the environment are required.

Next Steps

Before making a final registration decision on oxalic acid dihydrate, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

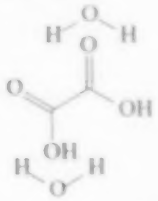
When the PMRA makes its registration decision, it will publish a Registration Decision on oxalic acid dihydrate (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

Science Evaluation

Oxalic Acid Dihydrate

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active substance	Oxalic Acid Dihydrate
Function	Acaride
Chemical name	
1. International Union of Pure and Applied Chemistry (IUPAC)	Ethanedioic acid, dihydrate
2. Chemical Abstracts Service (CAS)	Ethanedioic acid, dihydrate
CAS number	6153-56-6
Molecular formula	$C_2H_6O_6$
Molecular weight	126.07
Structural formula	
Purity of the active ingredient	99.65% nominal

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Product—Oxalic Acid Dihydrate Technical

Property	Test substance	Result
Colour and physical state	Oxalic acid	Transparent, colourless solid
Odour	Oxalic acid	Odourless
Melting range	Oxalic acid Oxalic Acid Dihydrate	187°C 101.5°C Both melts and decomposes, sublimation begins at 100°C
Boiling point or range	Oxalic Acid Dihydrate	149 - 160°C sublimes with partial decomposition
Specific gravity	Oxalic acid Oxalic Acid Dihydrate	1.9 1.65
Vapour pressure at 20°C	Oxalic acid	< 0.001 mm Hg
Ultraviolet (UV)-visible spectrum	Oxalic acid	Not expected to absorb UV at $\lambda > 350$ nm

Property	Test substance	Result
Solubility in water at 20°C	Oxalic acid	100 g/L
Solubility in organic solvents	Oxalic acid	Solvent — Solubility alcohol — 1 g / 2.5 mL glycerol — 1 g / 5.5 mL ether — 1 g / 100 mL insoluble in benzene, chloroform and petroleum ether
n-Octanol-water partition coefficient (K_{ow})	Oxalic acid	log K_{ow} = -0.81; -0.43
Dissociation constant (pK_a)	Oxalic acid	pK_{a1} = 1.46 pK_{a2} = 4.40
Stability (temperature, metal)	Oxalic acid	Normally stable. If heated to melting point sublimation and decomposition occurs. Bases – vigorous reaction may occur, yielding heat and pressure. Oxidizing agents (e.g. sodium chlorite, sodium hypochlorite) – may react violently or explosively. Silver – may form explosive silver oxalate. Alkali metals (e.g. sodium or potassium) – may react violently and produce flammable hydrogen gas. Iron and iron compounds (e.g. ferric acid) – may react rapidly to form ferric oxalate. Acid chlorides – may react vigorously producing toxic fumes.

End-Use Product—Oxalic Acid Dihydrate

Property	Result
Colour	Colourless
Odour	Odourless
Physical state	Solid
Formulation type	Soluble powder
Guarantee	99.65% nominal
Container material and description	Plastic screw top glass or HDPE containers, 0.5 kg to 25 kg
Specific gravity	1.65
pH of 0.1 M solution in water	1.3
Oxidizing or reducing action	The product is a medium strong acid which reacts vigorously with strong bases. Reacts violently with oxidants causing fire and explosion hazard.

Property	Result
Storage stability	Stable if stored in a cool, dry, well-ventilated area away from incompatible substances.
Corrosion characteristics	Not expected to be corrosive to the packaging material.
Explodability	If reacted with silver may form explosive silver oxalate.

1.3 Directions for Use

Oxalic Acid Dihydrate is used for the control Varroa mites in honeybee colonies using two different application methods. The first method is known as a solution or trickle treatment method, in which 35 g of Oxalic Acid Dihydrate per litre is dissolved in a 1:1 sugar/water solution and applied directly to the bees at a rate of 5 mL per bee-occupied space, up to a maximum of 50 mL per hive. The second application method is by vaporisation, which uses a specialised application device that heats and vaporises Oxalic Acid Dihydrate crystal at an application rate of 2.0 g Oxalic Acid Dihydrate per hive. Applications are made in the late fall to early spring, when little to no brood is present in the hive and honey supers are not in place.

1.4 Mode of Action

While the mode of action of oxalic acid solutions against Varroa destructor is not entirely understood, it appears to be mainly due to the low pH of the acid, which results in contact toxicity (physical injury of mites due to low pH). Due to the high disassociation constant of Oxalic Acid Dihydrate, even at very low concentrations Oxalic Acid Dihydrate in solution will result in a low pH value. With the trickle-method of application, the Oxalic Acid Dihydrate is directly applied to the infested bees. The bees can tolerate the concentration of oxalic acid in the applied solution, but the Varroa mites cannot. With the vaporisation method of application, oxalic acid dihydrate crystals are heated until they liquefy and vaporise. Oxalic acid vapour fills the hive and all the bees and hive interior surfaces are covered with a very thin layer of oxalic acid dihydrate crystals. While these fine crystals are tolerated by the bees, they are toxic to the Varroa mites.

2.0 Methods of Analysis

2.1 Methods for Analysis of the Active Ingredient

The methods for the analysis of the active ingredient and the impurities in Oxalic Acid Dihydrate Technical have not been provided. However, oxalic acid may be analysed using an HPLC method with UV detection. This is a well established method for which a description may be found in the public literature. Therefore, the submission of the methods has been waived.

2.2 Method for Formulation Analysis

The formulation of the end-use product, Oxalic Acid Dihydrate, is a repack of the technical product. Consequently the same analytical method is applicable to this product and it can be used as an enforcement analytical method.

2.3 Methods for Residue Analysis

Oxalic acid may be analyzed using an HPLC method with UV detection.

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for oxalic acid dihydrate was conducted by the PMRA, however elements of this review relied on evaluation reports (monographs) prepared by regulatory authorities with equivalent health assessment criteria and standards to those of the PMRA. Mainly, the PMRA relied, in part, on test data summaries in the U.S. Environmental Protection Agency's Reregistration Eligibility Document (U.S. EPA RED) on oxalic acid as well as the European Agency for the Evaluation of Medicinal Products' (EMEA) Committee for Veterinary Medicinal Products summary report on oxalic acid.

The database for Oxalic Acid Dihydrate is sufficiently complete (Tables 1 & 2, Appendix I), consisting of laboratory animal toxicity studies (acute oral and dermal), rationales to waive certain short-term and chronic test data requirements and data available in the scientific literature. Together, this information was used to assess the toxicological hazards of both the technical grade active ingredient (TGAI), Oxalic Acid Dihydrate Technical and its associated end-use product (EP), Oxalic Acid Dihydrate. Although the PMRA normally requires acute toxicity and irritation studies on both the TGAI and the EP, given that the formulation contains no formulants of toxicological concern, test data only on the TGAI was accepted by the PMRA to support the EP registration application. The overall scientific quality of the database is considered sufficient to characterize the toxicity of the TGAI and EP for the purposes of conducting a human health risk assessment when oxalic acid dihydrate is used for the control of Varroa mites on honeybees.

3.1.1 Acute Toxicity

Acute oral toxicity studies indicate that oxalic acid dihydrate is of moderate to high toxicity in rats with an LD_{50} of 475 mg/kg bw for males and 375 mg/kg bw for females. For dogs and cats oral toxic doses have been reported at 1000 mg and 200 mg, respectively. The main target organ is the kidney with primary effects being formation of calcium oxalate crystals associated with focal necrosis, mineralization and impairment of kidney function. Calcium depletion with sequelae of hypocalcemia has also been reported in animal studies with oxalic acid dihydrate. In dogs, when administered with approximately 40 mg/kg bw oxalic acid dihydrate by intravenous injection, 100% of animals died shortly after administration. Oxalate binds to blood calcium and induces neurotoxicity and cardiac arrest. Dermal toxicity of oxalic acid dihydrate is low with an

LD_{50} > 20,000 mg/kg bw in female rabbits. An inhalation LC_{50} was unavailable in the published literature, but the chemical nature of oxalic acid is such that it would be expected to cause severe irritation and damage to the respiratory tract on inhalation.

According to data available in the scientific literature, Oxalic Acid Dihydrate is moderately irritating when applied to the skin and severely irritating to the eyes. The pH of Oxalic Acid Dihydrate is 1.3, which suggests it is a corrosive compound. As detailed studies were not submitted by the applicant, classification of Oxalic Acid Dihydrate to the skin and eye is presumed to be corrosive. This conclusion is supported by available information on oxalic acid, including the reregistration findings of the U.S. EPA.

Although there was a lack of information with respect to oxalic acid dihydrate's potential as a dermal sensitizer, the long history of its use in a variety of industrial processes and consumer products, coupled with a general lack of medical reports regarding sensitization potential of oxalic acid, suggests that the Oxalic Acid Dihydrate Technical is not a dermal sensitizer.

3.1.2 Short-term Toxicity

Young adult Long-Evans rats were administered oxalic acid dihydrate in the diet at 0, 2.5, and 5.0% (estimated to be 0, 1.98, and 5.3 g/kg bw/day in females; 0, 1.78, and 5.3 g/kg bw/day in males) for 70 days. There was a statistically significant decrease in body weight in both the 2.5 and 5.0% dose groups ($p<0.001$) in males and females. The mortality rate for the 5.0% dose group was 25%, whereas the mortality rate for the 2.5% group was <10%. There were no clinical effects apparent in the 2.5% dose group, but pronounced effects were noted in both males and females in the 5.0% dose group, i.e., emaciated, stunted, gaunt with arched backs, disrupted estrous cycles as well as depressed thyroid function and thyroid weight. Gross pathology results demonstrated a lack of body fat and a minimal amount of adipose tissue adherent to visceral and endocrine tissue, as well as kidneys which were discoloured, brownish with roughened crinulated surfaces, abnormal notching on the edges and presence of small stones. The majority of these findings are consistent with emaciated animals, resulting from a significant loss of body weight and are not necessarily caused directly by oxalic acid dihydrate. The kidney pathology may have been due to oxalic acid dihydrate, especially given the presence of small stones which is consistent with the known renal effects of calcium oxalates.

Rats intravenously administered 25, 50 and 75 mg/kg bw/day of sodium oxalate for 2, 3 and 1 weeks, respectively exhibited hematuria, with increased excretion into urine of white blood cells, epithelia and casts. Histopathology findings of the kidney revealed some deposition of oxalate. These effects were indicative of mild nephrotoxicity due to tubular obstruction.

3.1.3 Metabolism

Oxalic acid is a ubiquitous substance endogenously produced in mammalian tissues and plants. Upon ingestion, oxalic acid chelates free calcium, iron and magnesium ions to deposit crystals of the corresponding oxalates, excess levels of which irritate the gastrointestinal tract and kidney tubules. Excess precipitation of calcium oxalate crystals in kidneys can lead to the formation of kidney stones. The majority of ingested oxalic acid is excreted as metal oxalates in the urine (at a rate of 25 mg daily) and feces.

3.1.4 Reproduction and Developmental Toxicity

A two-generation reproductive toxicity study with Oxalic Acid Dihydrate in CD-1 mice given doses of 0, 0.05, 0.1 and 0.2% in drinking water (corresponding to 89, 162 and 275 mg/kg/bw/day in males only) reported significantly decreased litters per mating pair, decreased live pup weight, and decreased prostate gland weight in the F0/F1 generations at the highest dose level. In the F1 generation, the total number of live pups decreased significantly as did prostate gland weight. Decreased water consumption was induced in the F1 generation 0.1% and 0.2% dose groups. In the F2 generation, relative kidney weights increased in females and incidence of abnormal sperm increased in males at the highest dose group. Oxalic Acid Dihydrate was concluded to be a weak reproductive toxicant in CD-1 mice at a dose of approximately 275 mg/kg bw/day. It did not induce overt teratogenic effects or postnatal toxicity. No effect on blood calcium concentration was observed. Oxalic acid dihydrate did appear to interfere with spermatogenesis. A no observed adverse effect level (NOAEL) value could not be derived, as data from the 0.05% and 0.1% dose groups were not recorded for the second generation.

3.1.5 Mutagenicity and Genotoxicity

Limited data are available to assess the mutagenic and genotoxic potential of oxalic acid. Anhydrous oxalic acid (99 %), in water as a solvent, was tested for bacterial mutagenicity using the Ames assay, on *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100. The concentrations tested were 0.0 – 6666.7 (µg/plate, with and without metabolic activation, that is, rat and hamster liver S-9, Aroclor 1254 induced). Results of the various Ames tests showed that Oxalic Acid Dihydrate is negative. Information available for the chromosome aberration test in vitro on mammalian Chinese hamster lung fibroblasts (CHL cells) showed that oxalic acid dihydrate is not considered to be clastogenic. There was a weak positive result in the chromosome aberration test with plant root meristem cells, but the relevance of this effect to mammalian systems is unknown. There is no information available that addresses the genotoxic effects of oxalic acid dihydrate in vivo.

Given the negative results from in vitro assays and data from chronic toxicity studies in rats that show no carcinogenic properties, no further genotoxicity studies were required by the PMRA. It is expected that, due to the long history of use in a number of manufacturing processes and consumer products, exposure to oxalic acid dihydrate resulting from the proposed pesticidal application in bee hives is unlikely to result in genotoxic effects.

3.1.6 Chronic Toxicity

In a two-year carcinogenicity study, Osborne-Mendel male and female rats were administered diet supplemented with 1000, 5000, 8000 and 12000 ppm of oxalic acid dihydrate, corresponding to 50 to 600 mg/kg bw/day. No effects were observed on body weight gain or food consumption during the first 52 weeks, and there was no significant difference between the mortality rate (recorded at 18 and 24 months) in treated and untreated control groups. Pathological findings included a slight periportal hypertrophy of the hepatic cells. Incidence of tumours was not significantly different among treated and untreated control groups, suggesting oxalic acid dihydrate is unlikely carcinogenic.

Given its corrosive properties, localized absorption of oxalic acid dihydrate from chronic dermal exposures may cause cyanosis and gangrenous tissue formation.

No information was available to address the immunotoxic or neurotoxic potential of oxalic acid dihydrate or its metal oxalates. Overdosage of oxalic acid dihydrate is expected to result in hypocalcemia-induced neurotoxic effects (both peripheral and central nervous system), including paraesthesia, tetany, seizures and depressed cardiac contractibility. However, in susceptible subpopulations such as individuals suffering from severely compromised kidney function or primary hyperoxaluria, hypocalcemia-induced neurotoxic sequelae are to be expected even following the intake of moderate amounts of oxalic acid dihydrate.

3.2 Occupational/Bystander Exposure and Risk Assessment

Oxalic acid is a commodity chemical that has many diverse, non-pesticidal, manufacturing and industrial uses, including use in textile printing and dyeing, bleaching of natural plant fibres such as straw and pulpwood, and in household cleansers for removing paint, varnish, rust or ink stains.

3.2.1 Occupational

There is a potential for exposure to the mixer, loader, and applicator when preparing and applying Oxalic Acid Dihydrate to bee hives. Occupational exposure to the Oxalic Acid Dihydrate is expected to be short-term in duration and predominantly by the dermal route during preparation and application activities. The product is to be applied to broodless or near broodless hives corresponding to late fall or early spring applications in Canada. Two application methods are proposed on the product label. The first is application by the vaporizer method which involves sublimation of solid Oxalic Acid Dihydrate using a heating device at the base of the sealed bee hive, and the second by the solution method which involves direct application of an Oxalic Acid Dihydrate-water-sucrose solution onto the bees in the hive. Additional exposure routes concern mainly the vaporization method and include inhalation, ingestion, and ocular contact with oxalic acid dihydrate vapour.

The maximum number of hives to be treated per day is expected to be approximately 200 for large bee keeping operations. The maximum amount of oxalic acid dihydrate applied per day could be as much as 280 – 350 g by the solution method and 400 g by the vaporization method.

Due to the corrosive nature of Oxalic Acid Dihydrate, and in the absence of a dermal absorption study, complete absorption via the dermal route is assumed by the PMRA.

Although a margin of exposure could not be estimated using available toxicological information, the label-required personal protective equipment and additional precautions regarding clean-up and repair activities and the requirement to work only under well-ventilated conditions are expected to minimize the exposure to oxalic acid dihydrate by workers. The product label requires applicators to wear eye goggles, dust mask, and chemical resistant gloves when handling Oxalic Acid Dihydrate. The label further requires applicators to wear a long-sleeved shirt and pants or coveralls to minimize dermal exposure during mixing and loading activities.

3.2.2 Bystander

While the corrosive nature of oxalic acid dihydrate places Oxalic Acid Dihydrate in the category of a skin and eye irritant, only workers will be permitted access to the treated areas, thus bystanders are not expected to be exposed to vapours or solutions of Oxalic Acid Dihydrate when it is applied to bee hives to control Varroa mites.

3.3 Dietary Exposure and Risk Assessment

3.3.1 Food

The product is not to be used when honey supers are in place, in order to prevent contamination of marketable honey or wax.

Oxalic acid is a natural constituent of honey, but the applicant was unable to provide a range of values of oxalic acid in Canadian honey. Information available from Europe indicates that oxalic acid is found normally in the range of 1 to 800 mg/kg, depending on the botanical source of the honey. Although no Canadian residue data were available from field trials, investigations in Europe using oxalic acid in a manner equivalent to proposed Canadian application methods, found no significant increase of oxalic acid in honey above naturally occurring levels. Concentrations of oxalic acid in honey measured after recommended and off-label treatment conditions were in the range of 5 to 289 mg/kg, well within the range of naturally occurring levels.

The majority of free oxalate anion present in honey will bind with calcium, which is also naturally found in honey, resulting in a compound which is poorly absorbed by the gastro-intestinal (GI) tract. Based on dietary consumption data in Europe, the daily intake of oxalic acid was estimated to be in the range of 5 to 500 mg, and exceeding 1000 mg for vegetarians. In plants, natural levels of oxalic acid range between 5 and 200 000 mg/kg dry weight.

The proposed use pattern is expected to result in a negligible increase in residues of oxalic acid dihydrate when compared to background levels naturally found in honey and especially when compared to the intake of oxalic acid from other food sources.

3.3.2 Drinking Water

The proposed use of Oxalic Acid Dihydrate in bee hives is not expected to result in environmental residues at any significant distance beyond the site of application and therefore unlikely to enter neighbouring aquatic environments. No risks are expected from exposure to residues of oxalic acid dihydrate via drinking water because exposure will be negligible to non-existent.

3.3.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

Use of Oxalic Acid Dihydrate against Varroa mites according to label directions is not expected to raise oxalic acid dihydrate residues above background levels naturally occurring in honey and beeswax, or result in environmental residues of any kind. In addition, there are currently no other registered pesticidal uses of oxalic acid. Therefore, exposure of potentially sensitive subpopulations, including infants, children and individuals with compromised kidney function, to oxalic acid dihydrate residues above those naturally found in honey and other foods is not expected to occur as a result of the proposed use of Oxalic Acid Dihydrate.

3.4 Maximum Residue Limits

Oxalic acid is a naturally occurring substance found in all mammalian species and in plants. Plant-based foods constitute the major source of dietary oxalic acid and, based on dietary intake estimates in Europe, consumption ranges from 5 to 500 mg/day and may occasionally exceed 1000 mg/day. Oxalic acid also occurs naturally in honey with an average content of approximately 200 mg/kg (range of 1 to 800 mg/kg). The dietary intake of oxalic acid dihydrate in honey from treated hives is not expected to contribute measurably to the overall intake of oxalic acid dihydrate in daily food from other sources. Therefore, the PMRA has concluded that there is no need to establish an MRL for oxalic acid dihydrate.

The European Medicines Agency (EMEA) Committee for Veterinary Medicinal Products did not require the establishment of an MRL for oxalic acid and the U.S. EPA exempted oxalic acid from the requirement of a tolerance. The Food Chemical CODEX has established an acceptable limit of 50 mEq/kg of honey for free acid.

3.5 Aggregate Exposure

The potential for dietary exposure of the general public to oxalic acid dihydrate residues resulting from its use in bee hives for the control of Varroa mites is not expected to raise background levels naturally found in honey and beeswax. Exposure via drinking water is not expected to occur from this use because use in bee hives is not expected to result in environmental residues of any sort. Non-occupational (i.e. residential) exposure is not expected to occur as a result of this use because there are no residential or any other uses registered for oxalic acid dihydrate.

The general public is exposed to oxalic acid by virtue of its natural occurrence in honey and other foods. Given that no appreciable increase in dietary or residential exposure relative to background levels is expected to occur from this use, the PMRA has determined that there is no unacceptable risk of harm expected from aggregate exposure to oxalic acid dihydrate residues.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Oxalic acid is a naturally occurring compound that transforms rapidly under environmental conditions. It occurs as the oxalate ion at environmentally relevant pHs (pKa1 = 1.25, pKa2 = 4.28); high mobility of the ion in soil is expected to occur based on an estimated K_{oc} value of 5. Volatilization from moist surfaces is not likely to be rapid, based on a low Henry's Law value 1.4 ×10-10 atm-m^2/mole at 25°C. Oxalic acid will readily dissolve in water because of its high solubility (100 g/L). Rapid anaerobic and aerobic biotransformation of oxalic acid in soil and water will occur.

Many plants naturally contain oxalic acid, particularly those belonging to the Oxalis (e.g. sorrels) and Rumex (e.g. wild rhubarb) families. Several mould species also produce oxalic acid. Anthropogenic inputs of oxalic acid into the environment may be from vehicle exhausts and pulp mill effluents. Oxalic acid has been found in bog sediments at concentrations of 1410 nmol/g (humic acid) and 3350 nmol/g (fulvic acid). In soil oxalic acid was found at 30 to 6 mg/kg in 0 and 540 cm depths, respectively, at a site in Germany. Lake sediment concentrations have been recorded in the range of 0.1 to 0.7 nmol/L of sediment. Oxalic acid was found in Los Angeles air samples at concentrations of 6.38 to 2.12 nmol/m^2.

With a bioconcentration factor predicted to be 0.6, oxalic acid is not expected to bioaccumulate.

4.2 Environmental Risk Characterization

Based on limited exposure, the chemical's natural occurrence and the likelihood for relatively rapid transformation under environmental conditions, the proposed use of Oxalic Acid Dihydrate is not expected to pose a significant risk to the environment. Therefore, further review of the environmental chemistry, fate, and toxicology of Oxalic Acid Dihydrate was not considered necessary.

5.0 Value

5.1 Effectiveness Against Pests

Thirteen efficacy study reports were submitted to demonstrate the efficacy Oxalic Acid Dihydrate for controlling Varroa mites in honeybee hives. Of these reports, five are from Canada and eight are from Europe. One other study, from the northern USA, was also considered in this review. Two application methods, trickle treatment and vaporisation, were tested. The trickle treatment method involves dissolving 35 g of Oxalic Acid Dihydrate in a litre of a 1:1

sugar/water solution, which was then applied directly to the bees at a rate of 5 mL per bee-occupied space, up to a maximum of 50 mL per hive. The vaporisation method uses a specialised application device that heats and vaporises oxalic acid dihydrate powder at an application rate of 2.0 g Oxalic Acid Dihydrate per hive. Applications are made in the late fall to early spring.

The rates tested in the submitted studies for trickle applications included rates ranging from 17.5 to 70 g Oxalic Acid Dihydrate per litre. Studies which used Oxalic Acid Dihydrate trickle applications in summer (August-September) all had very low efficacy as Oxalic Acid Dihydrate has no effect on Varroa in the brood. Therefore it is important that the colonies should be broodless or nearly broodless during treatments (i.e. late fall to early spring). All other studies tested late fall to early spring applications. Only one study tested an application with a 1:2 sugar/water solution (with 45 g Oxalic Acid Dihydrate /litre solution); all other studies testing trickle treatments used a 1:1 sugar/water solution. The result of this study indicated that lower sugar concentrations reduced efficacy. The submitted studies support an application of 5 mL of 35 g Oxalic Acid Dihydrate per litre of 1:1 sugar/water solution per occupied bee space per hive, up to a maximum of 50 mL per hive (depending on hive size/strength), with 90-99% control of Varroa mite. Submitted data also supports applications via the vaporisation method at a rate of 2.0 g per hive, with rates of control from 90.0 to 99.8%.

Several of the submitted studies tested bee tolerance and colony survival for trickle-treatments. There is some indication that under certain unfavourable conditions, higher concentrations of Oxalic Acid Dihydrate resulted in greater bee death and slower colony recovery compared to colonies not treated with Oxalic Acid Dihydrate. Generally, however, it appears that unless there are poor overwintering conditions, which affects all hives regardless of treatment, applications of 35 g Oxalic Acid Dihydrate/L does not have a great enough impact on bee mortality or survivorship to overcome the benefits of the high rate of Varroa mite control afforded by Oxalic Acid Dihydrate applied by the trickle method. As well, submitted data showed evidence that colonies do recover from losses due to Oxalic Acid Dihydrate trickle applications. All studies which tested for adverse effects due to applications of Oxalic Acid Dihydrate through vaporisation found no significant adverse effects in bee tolerance. As well, a follow-up study found that there were no adverse effects on either colony overwintering success or spring colony development from the application of Oxalic Acid Dihydrate by vaporisation.

The submitted data support both trickle and vaporisation application methods. Trickle treatment applications are supported for control of Varroa mites in bee hives with a solution of 35 g Oxalic Acid Dihydrate per litre of 1:1 sugar/water at an application rate of 5 mL per bee-occupied space (frame), up to a maximum application rate of 50 mL per hive. A warning must be included that under certain conditions, trickle treatments may result in bee mortality. Vaporisation treatments are supported by the submitted data for control of Varroa mites in bee hives at an application rate of 2 g Oxalic Acid Dihydrate powder per hive. Application directions should indicate that treatments may only occur in late fall or early spring, and care must be taken to ensure that no or very little brood is present. Applications must only be made after monitoring indicates they are necessary.

A summary of the supported uses of Oxalic Acid Dihydrate for the control of Varroa Mite in honeybee colonies of are outlined in Table 4 of the Appendix.

5.2 Sustainability

The use of control products such as oxalic acid dihydrate, which have little likelihood of resulting in the development of resistance in Varroa mite populations, will be a key part of the Integrated Pest Management of honeybee colonies, especially in light of resistance problems that are developing with the conventional chemical miticides which are currently in use.

5.2.1 Survey of Alternatives

There are three registered alternative control products for control of Varroa mite in honeybee hives: formic acid, coumaphos, and fluvalinate-tau.

5.2.2 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Based on the mode of action (physical injury of mites due to the low pH of the acid), the development of resistance to oxalic acid dihydrate is unlikely in Varroa mite populations. Oxalic acid dihydrate has been used in Europe for over ten years, with no evidence that mites have developed resistance.

5.2.3 Contribution to Risk Reduction and Sustainability

Oxalic acid dihydrate will contribute to sustainability, as it is compatible with current Varroa mite control products. Additionally, it will provide an important tool for sustainable management of Varroa mites, as resistance is unlikely to occur with this product.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances [those that meet all four criteria outlined in the policy, i.e. persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*].

During the review process, Oxalic Acid Dihydrate and its transformation products were assessed in accordance with the PMRA Regulatory Directive DIR99-03[5] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

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[5] DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

- Oxalic Acid Dihydrate does not meet the Track 1 criteria and will not form any transformation products which meet the Track 1 criteria. Oxalic acid is a naturally occurring substance and is not expected to be persistent or bioaccumulative in the environment.

6.2 Formulants and Contaminants of Health or Environmental Concern

Oxalic Acid Dihydrate Technical and Oxalic Acid Dihydrate end-use product do not contain any formulants or contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02[6].

7.0 Summary

7.1 Human Health and Safety

The available toxicological information on Oxalic Acid Dihydrate is of sufficient quality to identify the majority of toxic effects that could result from human exposure to the active ingredient. Oxalic acid dihydrate is corrosive to the skin and eyes, and is also highly irritating and damaging to the respiratory system if inhaled. It is of high acute oral toxicity and low acute dermal toxicity. Acute exposure can also cause stomach irritation, lowered calcium levels as well as effects to the nervous system and kidney damage. Short-term exposure via the diet showed decreased body weights, disrupted estrous cycles, depressed thyroid function and decreased thyroid weight. Metabolism studies showed that excess levels of oxalic acid dihydrate cause kidney damage in mammals. Chronic oral intake in animals also produces kidney damage and disturbances in the metabolism of calcium. A multigeneration mouse reproduction study showed reproductive effects and parental toxicity at the highest dose, but also showed oxalic acid dihydrate was not developmentally toxic (teratogenic).

Workers are not expected to be exposed to concentrations of Oxalic Acid Dihydrate of any consequence if the product label precautionary statements are observed. Bystanders are not expected to have access to treated areas.

The establishment of an MRL was not required for oxalic acid dihydrate, as the increase in residues in honey from pesticidal applications to bee hives is expected to be negligible compared to naturally occurring background levels.

7.2 Environmental Risk

Based on limited exposure, the chemical's natural occurrence and the likelihood for relatively rapid transformation under environmental conditions, the proposed use of oxalic acid dihydrate is not expected to pose a significant risk to the environment.

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[6] DIR2006-02, PMRA Formulants Policy.

7.3 Value

Oxalic Acid Dihydrate has value for control of Varroa mite in honeybee colonies. Evaluated data demonstrated that oxalic acid dihydrate can provide 90-99% control of Varroa mites in honeybee colonies when either the trickle treatment or vaporisation application methods are used when little to no honeybee brood is present in the hives (i.e. in the late fall to early spring).

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of Oxalic Acid Dihydrate Technical and Oxalic Acid Dihydrate, containing the technical grade active ingredient oxalic acid dihydrate, active ingredient to control Varroa mites in honeybee colonies.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

atm	atmosphere
bw	body weight
CAS	Chemical Abstracts Service
cm	centimetres
EP	End-Use Product
mEq	milliequivalent
g	gram(s)
HDPE	high-density polyethylene
Hg	mercury
HPLC	high-performance liquid chromatography
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram(s)
K_{oc}	organic-carbon partition coefficient
K_{ow}	*n*–octanol-water partition coefficient
L	litre(s)
LC_{50}	lethal concentration to 50%
LD_{50}	lethal dose to 50%
LOAEL	lowest observed adverse effect level
m^2	metre(s) squared
m^3	metre(s) cubed
mg	milligram
mL	millilitre
mm	millimetre(s)
MRL	maximum residue limit
NOAEL	no observed adverse effect level
PMRA	Pest Management Regulatory Agency
ppm	parts per million
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
U.S. EPA	United States Environmental Protection Agency
UV	Ultra violet

Appendix I Tables and Figures

Table 1 Acute Toxicity of Oxalic Acid Dihydrate and Its Associated End-use Product (Oxalic Acid Dihydrate)

Study Type	Species	Result	Comment	Reference
Acute Toxicity of Oxalic Acid Dihydrate (Technical) and End-Use Product Oxalic Acid Dihydrate				
Oral	Rat – Sprague-Dawley	LD50 (♀) = 375 mg/kg bw	High acute toxicity	1810581
Dermal	Rabbit – New Zealand white	LD50 (♀) > 20,000 mg/kg bw	Low acute toxicity	1810581
Inhalation	This data requirement was waived based on the chemical nature of oxalic acid dihydrate, which is expected to cause severe irritation and damage to the respiratory tract.			
Skin irritation	The pH of oxalic acid dihydrate is 1.3, suggesting a compound which is corrosive to the skin and to the eyes.		Extremely corrosive or irritating	966154
Eye irritation			Extremely irritating	966154
Skin sensitization	This data requirement was waived based on a long history of use in industrial processes and consumer products, a general lack of medical reports regarding the sensitizing potential of oxalic acid, and a pH < 2.			

Table 2 Short-term and Chronic Toxicity Profile of Technical Oxalic Acid Dihydrate

Study Type	Species	Results (mg/kg/day in M/F)	Reference
Short-term oral toxicity	Rats: Long-Evans Dose (♀) 0, 1.98, and 5.3 g/kg bw/day; (♂) 0, 1.78, and 5.3 g/kg bw/day	A 25 % mortality rate at the high dose groups and < 10 % in the mid-dose groups. Significant decrease in body weight in both the mid- and high-dose groups ($p < 0.001$). Gross pathology of the kidneys showed discolouration, roughened crinulated surfaces, abnormal notching on the edges, and the presence of small stones in both the mid- and high-dose groups may be a result of oxalic acid dihydrate toxicity, but study was not available to confirm this finding. A NOAEL and a LOAEL could not be determined from the available information.	966167
Short-term intravenous toxicity	Rats Dose 25, 50, and 75 mg/kg bw/day of sodium oxalate for 1, 2, and 3 weeks	Increased excretion of white blood cells, epithelia, and casts in the urine, and some oxalate deposition in the kidneys may be an indication of mild nephrotoxicity due to tubular obstruction. A NOAEL and a LOAEL could not be determined from the available information.	966156
Prenatal developmental toxicity	This data requirement was waived based on a long history of use in industrial processes and consumer products, a general lack of medical reports regarding prenatal developmental toxicity, and the availability of two-generation reproduction toxicity information.		

Study Type	Species	Results (mg/kg/day in M/F)	Reference
Two-generation reproduction	Mice: CD-1 Dose (♂ only) 0, 89, 162, and 275 mg/kg bw/day	Decrease in the size of the litter, decreased live pup weight, and decreased prostate weight in the high-dose group of the F0/F1 generations. Total number of live pups decreased, as well as prostate gland weight in the F1 generation. Relative kidney weights increased in the females and abnormal sperm increased in the males in the high-dose group of the F2 generation. Oxalic acid dihydrate appears to be a weak reproductive toxicant in mice in the high-dose group, based on a decrease in sperm in the F2 generation. There was no overt teratogenic or postnatal toxicity observed in any of the test groups. A NOAEL and a LOAEL could not be determined from the available information. Data was not provided for the low- and mid-dose groups of the F2 generation.	966167
Chronic/ Carcinogenicity (2-year dietary)	Rats: Osborne-Mendel Dose (♂♀) 50, 250, 400, and 600 mg/kg bw/day	No significant adverse effects were observed. The NOAEL and LOAEL could not be determined from the available information because a maximum tolerated dose was not reached in the treated groups.	966156
Reverse gene mutation assay	*Salmonella typhimurium* (strains TA 98, TA 100, TA 1535 and TA 1537) 0-6666.7 µg/plate; with and without activation	Negative	966167
In vitro mammalian chromosomal aberration	Chinese hamster lung fibroblasts (CHL cells)	Negative	966167
Metabolism	Unknown	Oxalic acid dihydrate quickly chelates with calcium, iron, and magnesium on ingestion and is poorly absorbed. The majority of the oxalic acid dihydrate is excreted as metal oxalates in the urine and feces.	966159 966167

Table 3 Supported uses of Oxalic Acid Dihydrate for the control of Varroa Mite in Honeybee Colonies.

Application Method	Application Rate	Application Timing and Details	General Comments
Solution (Trickle Treatment) Method	Apply at a rate of 5 mL of solution per occupied bee space to a maximum of 50 mL per colony, whether bees are in nucs, single, or multiple brood chambers.	Dissolve 35 g of Oxalic Acid Dihydrate in 1 litre of 1:1 sugar:water (weight:volume) solution. (NOTE: To completely dissolve Oxalic Acid Dihydrate, use warm syrup.) Smoke bees down from top bars, and use a syringe or applicator to trickle solution directly onto the bees in each occupied bee pace in each brood box. Under certain unfavourable conditions (e.g. weak colonies, unfavourable overwintering conditions), this application method may cause some bee mortality or overwintering bee loss.	CAUTION: Oxalic Acid may damage bee brood. Oxalic Acid will not control Varroa mites in capped brood. Use only in late fall or early spring when little or no brood is present. Do not use when honey supers are in place to prevent contamination of marketable honey.
Vaporisation Method	2.0 g of Oxalic Acid Dihydrate powder per hive.	Apply only to outdoor colonies with a restricted lower hive entrance. Seal all upper hive entrances and cracks with tape to avoid escape of oxalic acid vapour. When possible, treat while hives are wrapped to ensure they are properly sealed. Smoke bees up from the bottom board. Place 2.0 g Oxalic Acid Dihydrate powder into vaporizer. Follow the vaporiser manufacturer's directions for use. Insert the vaporizer apparatus through the bottom entrance. Apply heat until all Oxalic Acid Dihydrate has sublimated.	

Table 4 Alternatives

Use (label) Claim	Alternative Active
Control of Varroa mite in honeybee hives	Formic Acid
	Fluvalinate-tau
	Coumaphos

References

A. List of Studies/Information Submitted by Registrant

1.0 Chemistry

TGAI

PMRA #	Reference
966154	CHEMINFO: Oxalic Acid. www.intox.org/databank/documents/chemical/oxalicac/cie358.htm Retrieved: August 27, 2004. 13pp. Published, DACO: 2.14.1,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9,2.3.1,2.4,2.5,2.6,2.7,2.8,3.1.4,3.5.1,3.5.10,3.5.11,3.5.14,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,3.5.9,4.1,4.2.1,4.2.4,4.2.6,4.4.2,4.4.3,4.6 CBI
966156	Hazardous Substances Databank: Oxalic Acid. www.ccohs.ca. Retrieved June 28, 2004. 23pp. Published, DACO: 2.14.10,2.14.11,2.14.13,2.14.14,2.3.1,4.4.1,8.1,8.2.1,8.2.2.1,8.4.1,9.1 CBI
966159	Reregistration Eligibility Document. www.epa.gov/oppsrrd1/REDs/old_reds/oxalic_acid.pdf Retrieved June 28, 2004. Environmental Protection Agency, United States of America. 58pp Published, DACO: 12.5.4,12.5.8,12.7,2.11.1,2.11.2,2.11.3,3.2.1,4.1,4.2.1,4.2.3,4.3.2,4.3.5,4.4.1,4.5.1,4.5.2,4.5.9,4.6.3,4.7,7.2.4,8.1 CBI
1263986	Process for the Preparation of Oxalic Acid and Sodium Hydrogen Oxalate from Crude Sodium Oxalate. Canadian Patent 1314905, DACO: 2.11.1,2.11.2,2.11.3 CBI
1263987	Certificate of Analysis. www.univarcanada.com Retrieved June 20, 2004. 1p., DACO: 2.11.4,2.12.1,2.13.3 CBI
1263988	Specification Sheet. www.univarcanada.com Retrieved June 20, 2004. 1p., DACO: 2.12.2,2.15 CBI
1263989	2001, Sodium Hydroxide Titrations: Standard Operating Procedure; Quality Control. Sigma Aldrich, Sheboygan Canada, DACO: 2.13.1,2.13.2 CBI
1263990	2000, Nicolet Avatar ESP ESP FT-IR Sample Analysis; Quality Control. Sigma Aldrich, Sheboygan Canada, DACO: 2.13.2 CBI
1263991	2002, Melting Point Apparatus (Thomas Hoover Unimelt); Quality Control. Sigma Aldrich, Sheboygan Canada, DACO: 2.13.2 CBI
1263992	Jeanette G. Grasselli, Atlas Of Spectral Data and Physical Constants for Organic Compounds. CRC Press. Clevland, USA. P. B716, DACO: 2.14.12,8.2.1 CBI
1622413	certificate of analysis, DACO: 2.13.3 CBI
1622414	certificate of analysis, DACO: 2.13.3 CBI
1622415	certificate of analysis, DACO: 2.13.3 CBI
1622416	certificate of analysis, DACO: 2.13.3 CBI
1622417	certificate of analysis, DACO: 2.13.3 CBI
1658807	2008, 5 Batch Data, DACO: 2.13.3

EP

PMRA #	Reference
966154	CHEMINFO: Oxalic Acid. www.intox.org/databank/documents/chemical/oxalicac/cie358.htm Retrieved: August 27, 2004. 13pp. Published, DACO: 2.14.1,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9,2.3.1,2.4,2.5,2.6,2.7, 2.8,3.1.4,3.5.1,3.5.10,3.5.11,3.5.14,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,3.5.9,4.1,4.2.1,4.2.4,4.2.6,4.4.2,4.4.3,4.6 CBI
966159	Reregistration Eligibility Document. http://www.epa.gov/oppsrrd1/REDs/old_reds/oxalic_acid.pdf Retrieved June 28, 2004. Environmental Protection Agency, United States of America. 58pp Published, DACO: 12.5.4,12.5.8,12.7,2.11.1,2.11.2,2.11.3,3.2.1,4.1,4.2.1,4.2.3,4.3.2,4.3.5,4.4.1,4.5.1, 4.5.2,4.5.9,4.6.3,4.7,7.2.4,8.1 CBI
966029	Process For The Preparation Of Oxalic Acid And Sodium Hydrogen Oxalate From Crude Sodium Oxalate. Canadian Patents Database. Patent No CA 1314905. Published, DACO: 3.2.2 CBI
966030	Certificate of Analysis. www.univarcanada.com Retrieved Nov 20,2004. 1p. Not Published, DACO: 3.2.3,3.5.4 CBI
966031	Specification Sheet. www.univarcanada.com Retrieved Nov 20,2004. 1p. Not Published, DACO: 3.3.2 CBI
966032	Sodium Hydroxide Titrations: Standard Operating Procedure; Quality Control. Sigma Aldrich, Sheboygan Canada. 3pp. Published, DACO: 3.4.1 CBI
966036	Storage of Oxalic Acid Sucrose Solution. Swiss Bee Research Center, Liebefeld, Switzerland. 3pp. Published, DACO: 3.5.10,7.2.5,7.3
966025	Hazardous Substances Databank: Oxalic Acid. www.ccohs.ca. Retrieved June 28, 2004. 23pp. Published, DACO: 5.1,5.3

2.0 Human and Animal Health

PMRA #	Reference
966154	CHEMINFO: Oxalic Acid. www.intox.org/databank/documents/chemical/oxalicac/cie358.htm Retrieved: August 27, 2004. 13pp. Published, DACO: 2.14.1,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9,2.3.1,2.4,2.5,2.6,2.7, 2.8,3.1.4,3.5.1,3.5.10,3.5.11,3.5.14,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,3.5.9,4.1,4.2.1,4.2.4,4.2.6,4.4.2,4.4.3,4.6 CBI
966156	Hazardous Substances Databank: Oxalic Acid. www.ccohs.ca. Retrieved June 28, 2004. 23pp. Published, DACO: 2.14.10,2.14.11,2.14.13,2.14.14,2.3.1,4.4.1,8.1,8.2.1,8.2.2.1,8.4.1,9.1 CBI
966159	Reregistration Eligibility Document. http://www.epa.gov/oppsrrd1/REDs/old_reds/oxalic_acid.pdf Retrieved June 28, 2004. Environmental Protection Agency, United States of America. 58pp Published, DACO: 12.5.4,12.5.8,12.7,2.11.1,2.11.2,2.11.3,3.2.1,4.1,4.2.1,4.2.3,4.3.2,4.3.5,4.4.1,4.5.1, 4.5.2,4.5.9,4.6.3,4.7,7.2.4,8.1 CBI
966164	Material Safety Data Sheet. Univar Canada Tech Data, Dept. Richmond BC, Canada. 6pp., DACO: 0.9,4.1,5.1

966165 Oxalic acid residues in honey. Melliferae.V,lmkerei Fischermühle, 72348 Rosenfeld,Germany. 2pp. Published, DACO: 4.1,7.4,7.4.1

966166 Determination of residues in honey after treatments with formic and oxalic acid under field conditions. Apidologie 33:399- 409. Published, DACO: 4.1,7.4

966167 Health-based Reassessment of Administrative Occupational Exposure Limits: Oxalic Acid. The Hague, Health Council of the Netherlands, Netherlands. 18pp. Published, DACO: 4.1,4.2.1,4.2.3,4.2.5,4.3.1,4.3.5,4.4.1,4.5.1,4.5.6,4.6.1,4.6.2,4.6.3,4.6.5,4.7.1

966168 Oxalic Acid Content of Selected Vegetables. In Agricultural Handbook No 8-11: Vegetables and Vegetable Products. USDA, United States of America. 2pp. Published, DACO: 4.1,4.4.2,4.4.3

966169 Nanetti, A. et al., 2003, Oxalic Acid Treatments for Varroa Control (Review), Apiacta 38:81-87, DACO: 12.5.8,12.7

966170 2001, New Zealand Ministry Agriculture and Forestry, Oxalic Acid Registration Submission for Varroa Control. NZMAF. Wellington NZ pp 21, DACO: 12.5.8

3.0 Environment

PMRA # **Reference**

966154 CHEMINFO: Oxalic Acid. www.intox.org/databank/documents/chemical/oxalicac/cie358.htm Retrieved: August 27, 2004. 13pp. Published, DACO: 2.14.1,2.14.2,2.14.3,2.14.4,2.14.5,2.14.6,2.14.7,2.14.8,2.14.9,2.3.1,2.4,2.5,2.6,2.7,2.8,3.1.4,3.5.1,3.5.10,3.5.11,3.5.14,3.5.2,3.5.3,3.5.6,3.5.7,3.5.8,3.5.9,4.1, 4.2.1,4.2.4,4.2.6,4.4.2,4.4.3,4.6 CBI

4.0 Value

PMRA # **Reference**

966043 Évaluation de l acide oxalique et de l acide formique en traitement du Varroa destructor pendant la période estivale. Centre de recherche en sciences animales de Deschambault, Quebec. 29 pp. Published, DACO: 4.1,7.4.1,10.2.3.2

966056 Varroa control with oxalic acid: a new application. In Proceedings of European Working Group for Integrated Varroa Control, Bern, Switzerland, June 16, 2000. 6pp. Published, DACO: 5.2,10.2.3.1

966058 Oxalic acid treatment by trickling: field against Varroa destructor:recommendations for use in Central Europe and under temperate conditions. Bee World 83(2):51- 60. Published, DACO: 10.2.3.1,10.2.3.3,12.7

966060 Drip treatment with oxalic acid: tests 1999/2000 and recommendations for use in central Europe. Swiss Bee Research Centre, Liebefeld, Switzerland. 10pp. Published, DACO: 10.2.3.1,10.2.3.3

966061 Alternative Strategy in Central Europe for the Control of Varroa destructor in honeybee colonies. Apiacta 38:258-285: Published, DACO: 10.2.3.1,10.2.3.3

966062 Acaricidal effect of oxalic acid in honeybee(Apis mellifera) colonies. Apidologie 32: 333 340. Published, DACO: 10.2.3.3

966063 Efficacy and tolerability of an oxalic acid trickling treatment. In Proceedings of European Working Group for Integrated Varroa Control, Bern, Switzerland, June 16, 2000. 2pp Published, DACO: 10.2.3.3

966064 Vaporization of oxalic acid in a field trial with 1509 colonies. Presentation to European Working Group for Integrated Varroa Control, York UK June 2001.9pp, DACO: 10.3.2

966067 Oxalic Acid in Varroa Control. An overview of the last five years of experiments. Istituto Nazionale di Apicoltura. Bologna, Italy. 5pp. Published, DACO: 10.2.3.1,10.2.3.3

966070 Oxalic Acid Efficacy Against Varroa Mites in the Fall. 2002 and 2003. Ontario Tech Transfer Program, OBA. Guelph, Ontario, 7 pp. Published, DACO: 5.2,10.2.3.1,10.2.3.3

966072 Late Fall Efficacy of Oxalic Acid on Varroa Mites in Honeybee Colonies. 2001 and 2002 Trials. Ontario Tech Transfer Program, OBA, Guelph Ontario 4 pp. unpublished, DACO: 5.2,10.2.3.1,10.2.3.3

966074 Efficacy of Three Miticides (Oxalic acid, Formic acid. Apilife Var) on Varroa destructor and Acarapsis woodi in Honeybee Colonies in Canada. 8th European Meeting on integrated Varroa Control, Kirchain Germany-22-23May 2003, DACO: 5.2,10.2.3.1

966469 Efficacy of Three Miticides (Oxalic acid, Formic acid. Apilife Var) on Varroa destructor in Honeybee Colonies in Alberta. American Bee Journal. Submitted, DACO: 5.2,10.2.3.1,10.2.3.3

B. Additional Information Considered

i) Published Information

1.0 Human and Animal Health

PMRA #	Reference
1810547	C. Curtin et. al., 1955, The Metabolism of Ascorbic Acid-1-C and Oxalic Acid-C In the Rat, DACO: 4.5.9
1810554	2004 TLVs and BEIs - Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices, DACO: 4.8
1810556	2003, The European Agency for the Evaluation of Medicinal Products, Committee for Veterinary Medicinal Products - Oxalic Acid Summary Report, DACO: 4.8
1810564	M. Grant, 1962, Toxicology of the Eye, DACO: 4.8
1810573	G. Hathaway et. al., 1966, Chemical Hazards of the Workplace, DACO: 4.8
1810577	M. Goldman et. al., 1977, Effect of Dietary Ingestion of Oxalic Acid on Growth and Reproduction in Male and Female Long-Evans Rats, DACO: 4.3.1
1810581	E.H. Vernot et. al., 1977, Acute Toxicity and Skin Corrosion Data for Some Organic and Inorganic Compounds and Aqueous Solutions, DACO: 4.8
1810584	G. Clayton, 1982, Patty's Industrial Hygiene and Toxicology, DACO: 4.8

2.0 Value

Stanghellini and Raybold, Evaluation of selected biopesticides for the late fall control of Varroa mites in a northern temperate climate. American Bee Journal, 144:6, 2004, pp. 475-487.